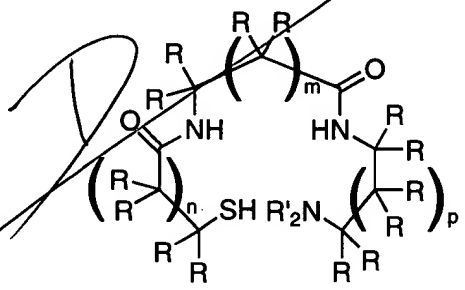
31 (amended). A composition of matter comprising, in combination, a monoamine, diamide, thiol-containing metal chelator covalently linked to a targeting moiety.

Add new claim 37 as set forth below.

37. A reagent according to claim 1, wherein the metal chelator has a formula:



REMARKS

Reconsideration of the application as amended is requested. The specification has been amended to correct typographical errors. The Examiner's attention is directed to formula I, appearing at page 10 and in claim 2, which has been amended to replace the "NH'_2" moiety with --NR'_2--. Support for this amendment appears throughout the application, in particular in formula III which appears at page 12 and in claim 3 and in formula IV which appears at page 13 and in claim 4. The dependencies of claims 3 and 4 from claim 2 are noted: the moiety which has been amended could not be NH_2 in claim 2 and be consistent with the recitations of NR^1R^2 in claims 3 and 4. No new matter has been added by virtue of the amendments to the specification.

Claim 9 has been cancelled for further prosecution in a continuation application. Claims 11-25, 27, 30, and 32-36 have been cancelled as being drawn to a non-elected invention. The claims have been amended to more particularly point out and distinctly claim the invention as embodied therein, as was requested by the Examiner in the Office Action dated November 13,

1996. Specifically, claims 1 and 2 have been amended to clarify the antecedent basis, and claims 3, 4, 5, 6, 7, 8, and 10 have been amended to correct the antecedent basis. Claim 2 has been further amended to recite only one formula, the second formula previously recited in claim 2 being re-presented in new claim 37. As discussed above in relation to the amendments to the specification, the formula of claim 2 has been amended to recite a NR'_2 moiety instead of a NH'_2 moiety. Claim 7 has been further amended to clarify the language relating to the sites of attachment of the chelator to the targeting moiety. Claim 8 has been further amended to clarify the language relating to the free amine. No new matter has been added by virtue of the amendments to the claims.

Rejections under 35 U.S.C. sec. 103

Claims 1-10, 26 and 31 stand rejected under sec. 103 as being unpatentable over Fritzberg et al. in combination with Rhodes et al. The Examiner takes the position that Fritzberg et al. and Rhodes et al. disclose formulae which may be substituted to yield various monoamine, diamide, thiol-containing metal chelating agents which may be linked to various specific targeting moieties to provide reagents useful for preparing a radiopharmaceutical agent. This rejection is respectfully traversed.

With respect for the Examiner's position at page 4 of the Office Action that the words "in combination with" denote an either/or situation, Applicants' undersigned attorney has not observed this interpretation of the words in nine years of patent prosecution practice. Applicants request a telephonic interview with the Examiner and his SPE to clarify this issue.

Submitted herewith is the Declaration of John Lister-James pursuant to 37 C.F.R. 1.132 (hereinafter the Lister-James Declaration), which discusses the cited references in detail and provides the following evidence.

- Fritzberg et al. does not teach how to make monoamine, diamide thiol-containing metal chelating agents and thus does not enable the presently claimed reagents.
- Even if Fritzberg et al. did enable production of the presently claimed reagents, formula I of Fritzberg et al. does not encompass the metal chelator claimed in claims 2-8 and 10.

- Fritzberg et al. teaches away from the chelating agents of claims 2-10, which are capable of forming an electrically neutral complex with metal ions such as oxotachnetium (V).
- The formulae depicting the metal ion-binding domains of Rhodes et al. cannot accurately be interpreted as disclosing the presently claimed invention.

The evidence provided in paragraph 4 of the Lister-James Declaration removes Fritzberg et al. as a reference against claims 2-8 and 10. Formula I of Fritzberg et al. does not have sufficient structural similarity to the formula of claims 2-8 and 10 to render those claims obvious, as a matter of law. *In re Deuel*, 34 U.S.P.Q.2d 1210, 1214 (Fed.Cir. 1995); *see also*, *In re Dillon*, 16 U.S.P.Q.2d 1897, 1901 (Fed.Cir. 1990). Withdrawal of the rejection of claims 2-8 and 10 over Fritzberg et al. is therefore respectfully requested.

Fritzberg et al.'s lack of disclosure of a method for making a monoamine, diamide thiol-containing metal chelator renders the free primary or secondary amine-containing chelators discussed at col. 4, lines 1-2 and at col. 9, lines 37-46 no more than research plans. It is notable that Fritzberg et al.'s disclosures of the free amine-containing chelators is limited to use with carbohydrates, in the context of the "post-formed chelate approach". Fritzberg et al.'s "post-formed chelate approach" is the only radiolabeling paradigm disclosed in the reference which is applicable to the presently claimed invention, since the metal chelator is necessarily covalently linked to the targeting moiety in all of the present claims. At col. 8, lines 45-51 Fritzberg et al. discloses that

> [e]xchange of radioactive metal from a labile inorganic complex to a chelator already conjugated to antibody (the post-formed approach) results in variable amounts of non-specifically bound radioactivity caused by electron donor groups (nitrogen, oxygen, and sulfur atoms) on the antibody or other large protein.

At col. 9, lines 24-35, Fritzberg et al. specifies that when the post-formed approach is used with polypeptides, an amide linkage is used between the polypeptide and "the carboxylic acid group". Chelating compounds having free amines are distinguished from those applied to polypeptides in

the disclosure appearing at col. 9, lines 37-46. This vague, limited, and confusing disclosure, combined with the lack of more than a suggested substitution in a generic formula, does not put the public in possession of an actual monoamine, diamide thiol-containing metal chelator. From the face of the reference, those of ordinary skill would have had no reason to pursue Fritzberg et al.'s disclosure to arrive at the presently claimed invention. Withdrawal of the rejection of claims 1, 26, 31 and 37 over Fritzberg et al. is respectfully requested.

The evidence provided in paragraphs 6 and 7 of the Lister-James Declaration removes Rhodes et al. as a reference against claims 1-8, 10, 26, 31, and 37. Withdrawal of the rejection of these claims over Rhodes et al. is therefore respectfully requested.

In light of the amendments and arguments set forth above, Applicants submit that the rejections contained in the final Office Action ofJune 13, 1997 should be withdrawn and that the present claims are in condition for allowance or appeal. Should the Examiner wish to discuss this application further, he is requested to contact the undersigned attorney.

Respectfully submitted,

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